PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 June 2000 (08.06.00)	
International application No. PCT/US99/25903	**Applicant's or agent's file reference** 2079.1028-002
International filing date (day/month/year) 03 November 1999 (03.11.99)	**Priority date** (day/month/year) 06 November 1998 (06.11.98)
Applicant ARNOLD, Lee, D. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 April 2000 (25.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US9925903

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2079.1028-002		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/25903	03/11/1999	06/11/1998
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant BASF AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/04/2000	29.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Escolar Blasco, P Telephone No. +49 89 2399 7331

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25903

I. Basis f th r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-40 as originally filed

Claims, No.:

1-29 with telefax of 22/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-29, in respect of IA.

because:

   ☒ the said international application, or the said claims Nos. 1-29 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	15,29
	No:	Claims	1-14, 16-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	see separate sheet

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Comments on item III

Claims 1-29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Comments on item V

1. Claims 1-14 and 16-28 would not meet the requirements of Articles 33(2) and (3) PCT, the reasons being as follows:

1.1 **D1** (WO 98 33917 A; 6 August 1998) describes polypeptides which act as VEGF or VEGF-C antagonists, as well as antibodies that bind to such polypeptides and can modulate the binding of the activating ligand to the KDR tyrosine kinase receptor (see page 7, line 28 to p.17, l.30; note that the cellular signalling function of KDR is thus inhibited).
D1 explains also that one of the biological activities of VEGF-C is increasing vascular permeability, and that polypeptides capable of binding to VEGFR-2 without stimulating receptor-mediated VEGF-C activity (i.e. without activating the receptor) are useful as antagonists of VEGF-C (see p.18, l.22 - p.19, l.7). Therefore, such peptides inhibit increased vascular permeability.
A polypeptide capable of specifically binding to KDR is also disclosed (see p.16, l.7-13).
D1 discloses additionally the treatment or prevention of eye diseases, infarction, breast cancer, edema and inflammation, among others (see p.19 l.8-25). Hence, it anticipates the subject-matter of claims 1-13, 16-25, 27 and 28.

1.2 **D2** (WO 98 11223 A; 19 March 1998) refers to monoclonal antibodies directed against an epitope of the extracellular domain of KDR, and the preparation of recombinant single-chain antibodies. The antibodies are useful in disease states such as tumors and rheumatoid arthritis (see the abstract and p.3).
Flt-1 is not mentioned, being the inhibition selective for KDR signalling function.
D2 is prejudicial for the novelty of claims 1-14 and 16-28.

1.3 D3-D8 are not considered relevant for the novelty of present claims 1-29, as they fail to disclose either the inhibition of vascular permeability, of the cellular signalling function of KDR, or both.

2. Claims 15 and 29, which refer to the coadministration of the inhibitor of the cellular signalling function of KDR with another agent selected from different functional groups, appear to lack inventive step.
Combining several agents is customary in the art, especially in the cases of tumor or inflammation. For such a combination to be considered as inventive, it should involve a surprising effect with respect to the separate administration of both compounds. As no such effect is showed in the application, no inventive effort seems to be present.

3. For the assessment of the present claims 1-29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Comments on item VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 98/58053	23.12.98	17.06.98	18.06.97
WO 97/17770	15.04.99	06.10.98	06.10.97
WO 99/55335	04.11.99	28.04.99	30.04.98
WO 99/17769	15.04.99	06.10.98	06.10.97

Comments on item VIII

1. Claims 1-29 are not supported by the description as required by Article 6 PCT: the present International Application relates to methods of treatment wherein the therapeutic agent is defined by its function (in the present case the inhibition of the cellular signalling function of KDR); this is not sufficient if the application discloses only isolated examples but fails to disclose any technical concept fit for generalisation, which would enable the skilled person to achieve the envisaged result without undue difficulty within the whole ambit of the claim containing the functional definition.
   In the present case, one single compound is cited (p.33 of the description), since the general mention in p.10-11 of antibodies, peptides, organic molecules, ribozymes and antisense polynucleotides cannot be considered as a complete disclosure.
   The tests of p.25-40 are intended for measuring the inhibitory activity of a given compound for different tyrosine kinases, as well as the selectivity for KDR tyrosine kinase. These tests do not give any hint, however, of which compounds could be tested, as they are written with vague references such as "suitable compounds of the present invention" or "a compound".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
2079.1001001		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/25903	03/11/1999	06/11/1998
Applicant		
BASF AKTIENGESELLSCHAFT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Present claims 1-30 relate to a use defined (inter alia) by reference to the following parameter(s):
P1: inhibition of the cellular signaling function of KDR; and the embodiments depending thereof in the dependent claims.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Present claims 1-30 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible (Cf. "administration of a compound to an individual", "organic molecules").

Present claims 16,30 relate to a pharmaceutical agent defined by reference to a desirable characteristics or properties, namely anti-endemic steroid, Ras inhibitor, anti-TNF agent, anti-IL1 agent, antihistamine, PAF-antagonist, COX-1 inhibitor, COX-2 inhibitor, NO synthase inhibitor, NSAID, PKC inhibitor, PI3 kinase inhibitor.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the example of the description (compound of the description, see page 33:
4,5-dihydro-3-pyridin-4-yl-1(2)H-benzo'g!indazole) in relation to the therapeutic applications as specified in claims 13,17,20, with due regard to the general idea underlying the present application.

Re claim 13, 20: "the administration of growth factors" was not

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

considered as a disease state.
Re claim 15, 27: "polynucletodies" was read as polynucleotides.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Vascular hyperpermeability and the subsequent events such as macular edema, retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, allergies, hypersensitive reactions, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, irritation or infection, erythema multiforme, edematous macules and other disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion, hypotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, can be inhibited by the administration of a compound that inhibits the enzyme activity of the VEGF tyrosine kinase receptor known as KDR tyrosine kinase.
The preferred compound 4,5-dihydro-3-pyridin-4-yl-1(2)H-benzo[g]indazole selectively inhibits the function of KDR tyrosine kinase but do not block the activity of Flt-1 tyrosine kinase which is another VEGF tyrosine kinase receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25903

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 17769 A (BASF AG ;BARLOZZARI TERESA (US); ARNOLD LEE D (US); XU YAJUN (US)) 15 April 1999 (1999-04-15) abstract page 9, line 10-20 page 10, line 1 -page 11, line 15 page 43, line 1-17 page 47, line 1-20; claims 1-10 ---	1-30
E	WO 99 55335 A (BASF AG ;RAFFERTY PAUL (GB); HOCKLEY MICHAEL (GB); TURNER ALLYSON) 4 November 1999 (1999-11-04) abstract; claims 1-14 page 11, line 10 -page 15, line 29 page 23, line 6-25 page 26, line 1-26 --- -/--	1-14,16, 17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2000	04/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 17770 A (BASF AG ;RAFFERTY PAUL (GB); HOCKLEY MICHAEL (GB); TURNER ALLYSON) 15 April 1999 (1999-04-15) abstract page 9, line 8 -page 11, line 21; claims 1-14	1-14, 17-29
P,X	WO 98 58053 A (KENDALL RICHARD L ;MAO XIANZHI (US); TEBBEN ANDREW (US); MERCK & C) 23 December 1998 (1998-12-23) the whole document	1,7,11, 12,14-29
X	WO 98 33917 A (UNIV HELSINKI LICENSING ;ALITALO KARI (FI); JOUKOV VLADIMIR (US);) 6 August 1998 (1998-08-06) abstract page 4, line 28 -page 25, line 27; claims 34-54	1-15, 17-29
X	WO 98 11223 A (MARTINY BARON GEORG ;SCHERING AG (DE); MENRAD ANDREAS (DE); TOTZKE) 19 March 1998 (1998-03-19) the whole document	1-15, 17-29
X	US 5 712 395 A (GAZIT AVIV ET AL) 27 January 1998 (1998-01-27) abstract; tables 4,5 column 3, line 19 -column 8, line 24	1-11,13, 14, 17-26, 28,29
X	WO 97 44453 A (GENENTECH INC ;DAVIS SMYTH TERRI LYNN (US); CHEN HELEN HSIFEI (US)) 27 November 1997 (1997-11-27) abstract page 32, line 12 -page 39, line 29	1-14, 16-29
X	FR 2 742 662 A (CENTRE NAT RECH SCIENT) 27 June 1997 (1997-06-27) abstract page 16, line 4 -page 19, line 3; claims 1-9	1-14, 16-29
X	WO 97 15662 A (RIBOZYME PHARM INC ;CHIRON CORP (US)) 1 May 1997 (1997-05-01) abstract page 5, line 23 -page 11, line 16; examples 5,6,10,11	1-14, 16-29
X	US 3 932 430 A (HABECK DIETMAR A ET AL) 13 January 1976 (1976-01-13) abstract column 11, line 8-49	1-14, 16-29

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2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 23 17 716 A (SANDOZ AG) 2 May 1974 (1974-05-02) abstract page 8, paragraphs 2,3	1-14, 16-29
A	US 3 843 664 A (COOMBS R ET AL) 22 October 1974 (1974-10-22) abstract	1-30
X	US 3 843 666 A (COOMBS R ET AL) 22 October 1974 (1974-10-22) abstract column 8, line 22-31	1-14, 16-29
X	US 3 843 665 A (COOMBS R ET AL) 22 October 1974 (1974-10-22) the whole document	1-14, 16-29

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/25903

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9917769 A	15-04-1999	AU 9691198 A	27-04-1999
WO 9955335 A	04-11-1999	NONE	
WO 9917770 A	15-04-1999	AU 9603998 A	27-04-1999
WO 9858053 A	23-12-1998	EP 1009814 A	21-06-2000
WO 9833917 A	06-08-1998	US 5776755 A	07-07-1998
		AU 711578 B	14-10-1999
		AU 6616996 A	26-02-1997
		EP 0842273 A	20-05-1998
		JP 11510689 T	21-09-1999
		AU 6262498 A	25-08-1998
		EP 0972028 A	19-01-2000
		CA 2228248 A	13-02-1997
		WO 9705250 A	13-02-1997
WO 9811223 A	19-03-1998	DE 19638745 A	12-03-1998
		AU 4622297 A	02-04-1998
		EP 0925359 A	30-06-1999
		HU 9904052 A	28-03-2000
		NO 991162 A	06-05-1999
		PL 332034 A	16-08-1999
US 5712395 A	27-01-1998	US 5763441 A	09-06-1998
		US 5792771 A	11-08-1998
		US 5981569 A	09-11-1999
		US 5849742 A	15-12-1998
		AU 1842395 A	29-08-1995
		CA 2182949 A	17-08-1995
		EP 0748219 A	18-12-1996
		JP 2000026393 A	25-01-2000
		JP 9508642 T	02-09-1997
		WO 9521613 A	17-08-1995
		US 5851999 A	22-12-1998
		AU 5562794 A	08-06-1994
		CA 2149298 A	26-05-1994
		CN 1094445 A	02-11-1994
		WO 9411499 A	26-05-1994
		EP 0669978 A	06-09-1995
		JP 8505763 T	25-06-1996
WO 9744453 A	27-11-1997	AU 717112 B	16-03-2000
		AU 3060497 A	09-12-1997
		EP 0907733 A	14-04-1999
		JP 2000502357 T	29-02-2000
		NZ 332779 A	29-06-1999
		US 5952199 A	14-09-1999
FR 2742662 A	27-06-1997	EP 0868434 A	07-10-1998
		WO 9723510 A	03-07-1997
WO 9715662 A	01-05-1997	AU 7666296 A	15-05-1997
		EP 0859837 A	26-08-1998
US 3932430 A	13-01-1976	AU 4765672 A	26-04-1974
		BE 797964 A	09-10-1973

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/25903

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3932430 A		BE 806671 A	29-04-1974
		BE 789948 A	11-04-1973
		DE 2317716 A	02-05-1974
		DE 2249644 A	19-04-1973
		FR 2157852 A	08-06-1973
		NL 7213549 A	17-04-1973
		NL 7304722 A	02-05-1974
		DD 100256 A	12-09-1973
		JP 48044254 A	26-06-1973
		ZA 7207315 A	28-08-1974
		DD 105225 A	12-04-1974
DE 2317716 A	02-05-1974	US 3932430 A	13-01-1976
		AU 4765672 A	26-04-1974
		BE 797964 A	09-10-1973
		BE 806671 A	29-04-1974
		BE 789948 A	11-04-1973
		DD 100256 A	12-09-1973
		DE 2249644 A	19-04-1973
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		JP 48044254 A	26-06-1973
		NL 7213549 A	17-04-1973
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US 3843666 A	22-10-1974	NONE	
US 3843665 A	22-10-1974	NONE	

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(71) Applicant *(for all designated States except US)*: BASF AKTIENGESELLSCHAFT [DE/DE]; D–67056 Ludwigshafen (DE).

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(74) Agents: WAGNER, Richard, W. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).

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(54) Title: INHIBITION OF THE FORMATION OF VASCULAR HYPERPERMEABILITY

(57) Abstract

Vascular hyperpermeability and the subsequent events such as macular edema, retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, allergies, hypersensitive reactions, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, irritation or infection, erythema multiforme, edematous macules and other disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion, hyotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, can be inhibited by the administration of a compound that inhibits the enzyme activity of the VEGF tyrosine kinase receptor known as KDR tyrosine kinase. The preferred compound 4,5-dihydro-3-pyridin-4-yl-1(2)H-benzo[g]indazole selectively inhibits the function of KDR tyrosine kinase but do not block the activity of Flt-1 tyrosine kinase which is another VEGE tyrosine kinase receptor.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25903

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 17769 A (BASF AG ;BARLOZZARI TERESA (US); ARNOLD LEE D (US); XU YAJUN (US)) 15 April 1999 (1999-04-15) abstract page 9, line 10-20 page 10, line 1 -page 11, line 15 page 43, line 1-17 page 47, line 1-20; claims 1-10 ---	1-30
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2000	04/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

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INTERNATIONAL SEARCH REPORT

Ir. .tional Application No
PCT/US 99/25903

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 25903

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Present claims 1-30 relate to a use defined (inter alia) by reference to the following parameter(s):
P1: inhibition of the cellular signaling function of KDR; and the embodiments depending thereof in the dependent claims.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Present claims 1-30 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible (Cf. "administration of a compound to an individual", "organic molecules").

Present claims 16,30 relate to a pharmaceutical agent defined by reference to a desirable characteristics or properties, namely anti-endemic steroid, Ras inhibitor, anti-TNF agent, anti-IL1 agent, antihistamine, PAF-antagonist, COX-1 inhibitor, COX-2 inhibitor, NO synthase inhibitor, NSAID, PKC inhibitor, PI3 kinase inhibitor.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the example of the description (compound of the description, see page 33:
4,5-dihydro-3-pyridin-4-yl-1(2)H-benzo'g!indazole) in relation to the therapeutic applications as specified in claims 13,17,20, with due regard to the general idea underlying the present application.

Re claim 13, 20: "the administration of growth factors" was not

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

considered as a disease state.
Re claim 15, 27: "polynucletodies" was read as polynucleotides.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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US 3843665 A	22-10-1974	NONE	

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(75) Inventors/Applicants *(for US only)*: ARNOLD, Lee, D. [CA/US]; 216 Ruggles Street, Westborough, MA 01581 (US). BOUSQUET, Peter, F. [US/US]; 39 Cross Road, Hubbardston, MA 01452 (US).

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Published
Without international search report and to be republished upon receipt of that report.

(54) Title: INHIBITION OF THE FORMATION OF VASCULAR HYPERPERMEABILITY

(57) Abstract

Vascular hyperpermeability in individuals is a prelude to a number of physiological events that are often deleterious. Among these events is the formation of edema, diapedesis, aberrant trans–endothelial exchange, extravasation, exudation and effusion, matrix deposition (often with abnormal stromal proliferation) and vascular hypotension. Vascular hyperpermeability and the subsequent events can be inhibited by the administration of a compound that inhibits the enzyme activity of the VEGF tyrosine kinase receptor known as KDR tyrosine kinase. Preferred administered compounds selectively inhibit the function of KDR tyrosine kinase but do not block the activity of Flt–1 tyrosine kinase which is another VEGF tyrosine kinase receptor.

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CLAIMS

What is claimed is:

1. A method of inhibiting vascular hyperpermeability in an individual comprising the inhibition of the cellular signaling function of KDR.

2. The method of Claim 1 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.

3. The method of Claim 1 wherein said cellular signaling function of KDR is stimulated by the binding of an activating ligand to the receptor portion of KDR.

4. The method of Claim 3 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.

5. The method of Claim 1 wherein said inhibition of the cellular signaling function of KDR is a process selected from the group consisting of blocking the production of an activating ligand, modulating the binding of the activating ligand to the KDR tyrosine kinase receptor, disrupting the dimerization of the receptor, blocking KDR trans-phosphorylation, inhibiting the activity of the KDR tyrosine kinase, impairing the recruitment of intracellular substrates of KDR, and interrupting the downstream signaling initiated by the phosphorylation activity of the KDR tyrosine kinase.

6. The method of Claim 5 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.

7. The method of Claim 1 wherein said inhibition occurs by the administration of a compound to said individual.

8. The method of Claim 7 wherein said compound inhibits the catalytic kinase activity of said KDR.

9. The method of Claim 7 wherein said compound is an antagonist of KDR tyrosine kinase activation.

10. The method of Claim 7 wherein said compound selectively inhibits the phosphorylation of KDR kinase substrates.

11. The method of Claim 7 wherein said compound is selective for said KDR tyrosine kinase.

12. The method of Claim 11 wherein said compound is selected from the group consisting of peptides, antibodies and organic molecules, wherein said compound binds to said KDR tyrosine kinase.

13. The method of Claim 12 wherein the administration of said compound inhibits the formation of a disease state selected from the group consisting of macular edema, aphakic/pseudoaphakic cystoid macular edema, retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, tissue edema at sites of trauma and allergic inflammation, allergies, hypersensitive reactions, polyp edema at sites of chronic inflammation, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, inhalation burn injury, skin burns, blistering associated with sunburn, irritation or infection, erythema multiforme, edematous macules and other skin disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis,

ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion, hypotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, and the administration of growth factors.

14. The method of Claim 11 wherein adverse effects associated with an alteration in the cellular signaling function of tyrosine kinases other than KDR are avoided when said compound is administered.

15. The method of Claim 7 wherein said compound is selected from the group consisting of single-chain antibodies, KDR-specific ribozymes and anti-sense polynucletodies, wherein said compound is introduced or produced intracellularly thereby inhibiting the proper presentation of functional KDR tyrosine kinase.

16. The method of Claim 7 wherein said compound is administered in combination with a pharmaceutical agent selected from the group consisting of an anti-endemic steroid, a Ras inhibitor, anti-TNF agents, anti-IL1 agents, an antihistamine, a PAF-antagonist, a COX-1 inhibitor, a COX-2 inhibitor, a NO synthase inhibitor, a nonsteroidal anti-inflammatory agent (NSAID), a PKC inhibitor and a PI_3 kinase inhibitor.

17. A method of inhibiting a physiological process or state in an individual, said physiological process or state selected from the group consisting of edema formation, diapedesis, extravasation, effusion, exudation, ascites formation, matrix deposition and vascular hypotension, wherein said inhibiting comprises the administration of a compound that inhibits the cellular signaling function of KDR.

18. The method of Claim 17 wherein said compound is selective for said KDR tyrosine kinase.

19. The method of Claim 18 wherein said compound is selected from the group consisting of peptides, antibodies and organic molecules, wherein said compound binds to said KDR tyrosine kinase.

20. The method of Claim 19 wherein the administration of said compound inhibits the formation of a disease state selected from the group consisting of macular edema, aphakic/pseudoaphakic cystoid macular edema, retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, tissue edema at sites of trauma and allergic inflammation, allergies, hypersensitive reactions, polyp edema at sites of chronic inflammation, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, inhalation burn injury, skin burns, blistering associated with sunburn, irritation or infection, erythema multiforme, edematous macules and other skin disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion, hypotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, and the administration of growth factors.

21. The method of Claim 17 wherein said compound inhibits the catalytic kinase activity of said KDR.

22. The method of Claim 17 wherein said compound is an antagonist of KDR tyrosine kinase activation.

23. The method of Claim 17 wherein said compound selectively inhibits the phosphorylation of KDR kinase substrates.

24. The method of Claim 17 wherein said compound is selective for said KDR tyrosine kinase.

25. The method of Claim 17 wherein said cellular signaling function of KDR is stimulated by the binding of an activating ligand to the receptor portion of KDR.

26. The method of Claim 25 wherein said compound is selective for said KDR tyrosine kinase.

27. The method of Claim 17 wherein said compound is selected from the group consisting of single-chain antibodies, KDR-specific ribozymes and anti-sense polynucletodies, wherein said compound is introduced or produced intracellularly thereby inhibiting the proper presentation of functional KDR tyrosine kinase.

28. The method of Claim 17 wherein said inhibition of the cellular signaling function of KDR is a process selected from the group consisting of blocking the production of an activating ligand, modulating the binding of the activating ligand to the KDR tyrosine kinase receptor, disrupting the dimerization of the receptor, blocking KDR trans-phosphorylation, inhibiting the activity of the KDR tyrosine kinase, impairing the recruitment of intracellular substrates of KDR, and interrupting the downstream signaling initiated by the phosphorylation activity of the KDR tyrosine kinase.

29. The method of Claim 17 wherein adverse effects associated with an alteration in the cellular signaling function of tyrosine kinases other than KDR are avoided when said compound is administered.

30. The method of Claim 17 wherein said compound is administered in combination with a pharmaceutical agent selected from the group consisting of an anti-endemic steroid, a Ras inhibitor, anti-TNF agents, anti-IL1 agents, an antihistamine, a PAF-antagonist, a COX-1 inhibitor, a COX-2 inhibitor, a NO synthase inhibitor, a nonsteroidal anti-inflammatory agent (NSAID), a PKC inhibitor and a PI_3 kinase inhibitor.

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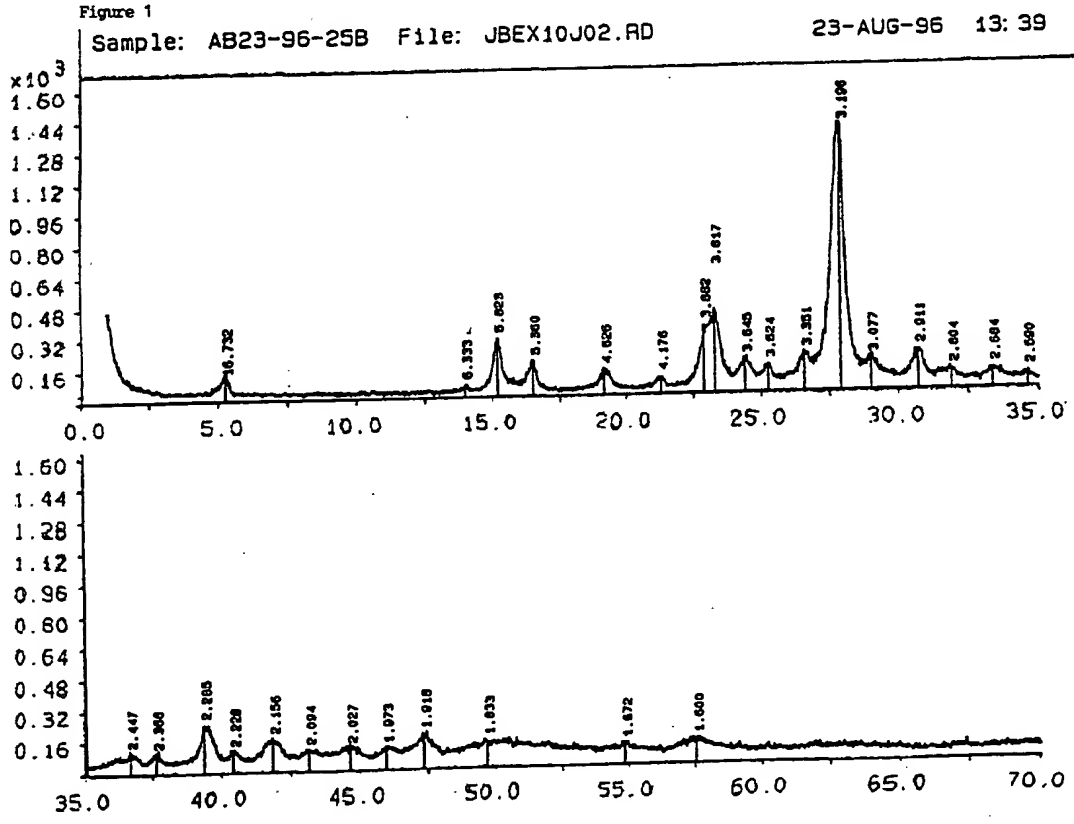
(54) Quinacridone pigment

(57) A new polymorphic form of 2,9-dichloroquinacridone having improved pigmentary properties and a method of forming said 2,9-dichloroquinacridone comprising the step of ring closure of appropriately substituted terephthalic acid in sulphuric acid.

Figure 1



EP 0 863 186 A1

Description

This invention relates to quinacridone pigments and a process of producing the same.

Quinacridone pigments are well known organic pigments which are particularly useful as colourants for high molecular weight organic materials.

Of the quinacridone pigments the di-substituted pigments, more particularly 2,9-dichloroquinacridone, are most notable for their pigmentary properties. 2,9-dichloroquinacridone is known to exist in three different polymorphic forms and it is known that each of the particular polymorphic forms have different pigmentary properties. In fact, the polymorphic form displays the best pigmentary properties.

It has now been found that a new polymorphic form of 2,9-dichloroquinacridone can be formed by a synthesis utilizing concentrated sulphuric acid.

The invention provides in one of its aspects a polymorphic form of 2,9-dichloroquinacridone having an x-ray diffraction pattern which comprises a major reflection corresponding to an interplanar spacing (d-value) of 3.20 Angstroms and an associated double glancing angle (Grade 2θ) of 27.9.

The new polymorphic form of 2,9-dichloroquinacridone is characterized by a number of reflections in its x-ray diffraction pattern which are not all found in the other known forms of this pigment. They include those reflections having the following interplanar spacings (d-value) and double glancing angles (Grade 2θ):

d-Value (Angstroms)	Grade 2θ
16.73	5.3
6.33	14.0
5.82	15.2
5.36	16.5
4.62	19.2
4.18	21.3
3.88	22.9
3.81	23.3
3.64	24.4
3.52	25.3
3.35	26.6
3.19	27.9
3.08	29.0
2.91	30.7
2.80	31.9
2.68	33.4
2.45	36.7
2.39	37.6
2.28	39.4

It will be understood that the figures recited above for the d-value and the double glancing angle are of course subject to fluctuation due to experimental error of +/- 0.1 (double glancing angle)

The invention provides in another of its aspects a process of making a 2,9-dichloroquinacridone comprising the step of reacting 2,5-di(4-chloroanilino)terephthalic acid in concentrated sulphuric acid.

The term "concentrated sulphuric acid" includes the acid at a strength of 90 to 95%, especially 92%.

The reaction is carried out at elevated temperatures, between 100 to 130°C, more preferably at 110°C.

The 2,5-di(4-chloroanilino)terephthalic acid starting material can be conveniently formed from dimethyl succinylosuccinate and 4-chloroaniline according to conventional syntheses employing commonly available reagents.

Preferably the 2,9-dichloroquinacridone formed according to the afore-mentioned reaction is filtered and washed salt-free with water before optionally being dried under vacuum at elevated temperature and optionally used as wet cake.

The 2,9-dichloroquinacridone so formed is in a crude form and is generally not possessed of the requisite desirable pigmentary properties. Accordingly, the crude quinacridone has to be processed further to obtain its desirable pigmentary properties. In a process according to the invention, the crude 2,9-dichloroquinacridone once formed is further processed by milling. Milling is preferably carried out using a ball-mill according to a procedure known in the art. The grinding action is carried out using, e.g. glass balls having a diameter of from 0.6 mm to 0.9 mm.

The 2,9-dichloroquinacridone pigment according to the invention can be applied to polymeric materials and displays better purity of nuance than heretofore achievable for the quinacridone pigments.

The term "polymeric materials" includes solvent-containing and solvent-free plastics materials, e.g. polyolefin, PVC, polystyrene and acrylic, polyester, alkyd or polyurethane lacquers.

There now follows a series of examples which serve to illustrate the invention.

EXAMPLE 1

Synthesis of 2,5-di(4-chloroanilino)terephthalic acid

A four-necked flask equipped with thermometer, stirrer and condenser is flushed with nitrogen and then charged with 228.2 parts of dimethyl succinylosuccinate, 267.8 parts of 4-chloroaniline and 3.3 parts of 65% sulphuric acid in 890 parts of n-butanol. The reaction mixture is stirred and heated to 110 to 115°C for 3 hours. During this time, 222.5 parts of n-butanol are allowed to distil over and are condensed for later use. After cooling the reaction mixture to 105°C, the n-butanol is returned to the reaction mixture followed by 5.3 parts of triethylamine and the condenser is replaced with a reflux condenser. The mixture is cooled to 90°C, 150.3 parts of powdered sodium m-nitrobenzene sulphonate is added

over a 10 minute period and the mixture heated to reflux. A dropping funnel is introduced to the apparatus and 392.0 parts of 30% sodium hydroxide is added dropwise over a one hour period into the reaction mixture. Refluxing is continued for 2 hours. Thereafter the reflux condenser is replaced with a condenser and 1760 parts of water are added dropwise to the reaction mixture to allow for azeotropic distillation of the n-butanol. The content of the flask is cooled to 70°C and the pH is adjusted to 5 with 304 parts of 35% hydrochloric acid. The resulting slurry is filtered, washed with hot water until the filtrate has a pH of 5 and dried conventionally under vacuum to yield 389 parts of the title compound.

EXAMPLE 2

Synthesis of 2,9-dichloroquinacridone

To 937 parts of 92% sulphuric acid at 110°C are added over a period of 3 hours 300 parts of 2,5-di (4-chloroanilino)terephthalic acid. The resultant mixture is heated for 12 hours at 130°C. The acid strength is reduced to 75% with the dropwise addition of 203 parts 33% sulphuric acid. The temperature of the resulting suspension is allowed to rise over the next 3 hours to 30°C. The solids in the reaction mixture are collected by filtration and washed with 1000 parts of sulphuric acid (75%), 2000 parts of water, 83.2 parts of ammonia (25%) and 2000 parts of water to obtain 385 parts of wet cake which is optionally oven dried under vacuum to yield 224.9 parts of crude 2,9-dichloroquinacridone.

Milling of the crude 2,9-dichloroquinacridone

A 0.5 liter jar is charged with 17.1 parts of crude 2,9-dichloroquinacridone wet-cake (58.4% = 10g 100%), 30 parts of sodium chloride, 150 parts of acetone and 500 parts of glass beads (diameter 0.6 to 0.9 mm). The jar is sealed and rotated on a roller mill for 72 hours. The mixture is then sieved to separate the balls, filtered and washed with 2000 parts of water. The resultant pigment is dried under vacuum at 100°C.

The resultant pigmentary form is characterized by its x-ray diffraction pattern which is shown in figure 1 and figure 2. The x-ray diffraction pattern can be compared with the x-ray diffraction pattern of the pigmentary form obtained by cyclisation in polyphosphoric acid according to a process described in GB 1 868 360 and subjected to the milling step described above, see figure 3 and figure 4.

Cyclisation of 2,5-di(4-chloroanilino)terephthalic acid in polyphosphoric acid as described in the following documents GB 1 868 360, US 3 257 405, JP 63 199 769 and US 5 496 405 represent the state of the art methods of obtaining 2,9- dichloroquinacridone.

Figure 1 shows the x-ray diffraction pattern of the pigmentary form of 2,9-dichloroquinacridon formed according to the methodology of Example 2. The numerical values associated with each peak represent the interplanar spacings in Angstroms.

Figure 2 shows the x-ray diffraction pattern of the pigmentary form of 2,9-dichloroquinacridone formed according to the methodology of Example 2. The numerical values associated with each peak represent the double glancing angles.

APPLICATION EXAMPLE A

The following experiment is carried out on a pigment form obtained according to the procedure of Example 2 and also on a commercial 2,9- dichloroquinacridone pigment Cinquasia Magenta RT-343D.

An Alkyd-melamine-formaldehyde (AMF) resin coating lacquer (ratio of coloured pigment (of Example 2) to white pigment is 1:10) was made according to the following procedure in accordance with the standard DIN 53235-1.

8 parts of the pigment obtained according to the procedure of Example 2, 100 parts of clear AMF (BASF FF 68-0102 14071) and 250 parts of glass pearls are ground over a 40 minute period in a Skandex stirrer. 3 parts of the resultant mixture are dispersed in 25 parts of AMF-white (BASF FD 68-0410 11074). The resultant dispersion is sprayed on to a white carton paper, allowed to air-dry for 10 minutes and then oven-dried for a further 30 minutes at 80°C. Using a colour spectrophotometer Minolta CM-508i, the L, a, b, C and H colour spacings are measured according to the standard DIN 55986 and 6174/CIELAB 76.

The above-described procedure was repeated for the 2,9- dichloroquinacridone pigment Cinquasia Magenta RT-343D and it is found to have the following CIELAB values:

L* = 58.3
a* = 34.2
b* = -16.1
C* = 37.8
H* = 334.8

whereas the pigmentary form produced according to the process described in Example 2 is found to have the following CIELAB values:

L* = 58.9
a* = 37.4
b* = -14.5
C* = 37.8
H* = 334.8

The colourimetric difference is therefore :

DC* = 2.23
DH* = 2.54
DE* = 3.38 (DE* is the total difference in the colour change.)

APPLICATION EXAMPLE B

The procedure described in Application Example A is followed using a pigment form obtained according to Example 7 in GB 1 868 360 (which has been subjected to the milling process described in Example 2 of this invention) in a lacquer as described in Application Example A. The pigment has been found to have the following CIELAB values:

L* = 57.0
a* = 36.3
b* = -15.9
C* = 39.7
H* = 336.3

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DC* = 0.82
DH* = 0.56
DE* = 1.00

APPLICATION EXAMPLE C

According to the standard DIN 8780/2 an AMF resin coating lacquer was made up as follows:

8 parts of pigment obtained according to Example 2, 100 parts of clear AMF (BASF FF 68-0102 14071) and 250 parts of glass pearls are ground over 40 minutes in a Skandex stirrer. 5 parts of this mixture are dispersed with 5 parts of clear AMF (BASF FF 68-0102 14071). The resulting dispersion is sprayed on to a sheet, allowed to air-dry for 10 minutes and then oven dried for 30 minutes at 80°C.

The L, a, b, C, H colour space values are measured according to the standards DIN 55986 and 6174/CIELAB 76 as described in Application Example A.

The experiment is repeated using Cinquasia Magenta RT-343D in a lacquer as described above and it has been found to have the CIELAB following values:

L* = 30.0
a* = 23.4
b* = 4.1
C* = 23.8
H* = 10.0

The pigment prepared according to the Example 2 in a lacquer as described above, has been found to have the following CIELAB values:

L* = 35.6
a* = 38.5
b* = 6.2
C* = 39.0
H* = 9.1

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DL* = 5.60
DC* = 15.77
DH* = -0.40
DE* = 16.74

APPLICATION EXAMPLE D

The pigment prepared according to the Example 7 of GB 1 868 360 (which has been subjected to the milling process described in Example 2 of this invention) in a lacquer as described in Application Example C has been found to have the following CIELAB values:

L* = 31.2
a* = 26.5
b* = 1.3
C* = 26.5
H* = 2.9

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DL* = 1.25
DC* = 2.76
DH* = -3.13
DE* = 4.36

APPLICATION EXAMPLE E

According to the standard DIN 53775B, the preparation of 0.6% coloured PVC sheet is performed as follows:

100.0 parts of PVC-white (5% TiO_2) are mixed with 0.6 part of the pigment of Example 2 for about 2 minutes. The resulting mixture is passed between two rollers in a rolling mill for 5 minutes, 26 rpm to form a sheet. One of the roller is at a temperature of 178°C and the other is at 163°C. The sheet so obtained is re-rolled at a temperature of 80°C and then pressed between two polished sheets for 0.5 minutes at 165°C.

The L, a, b, C, H colour space values are measured according to the standards DIN 55986 and 6174/CIELAB 76 as described in Application Example A.

The experiment is repeated using Cinquasia Magenta RT-343D and it has been found to have the following CIELAB values:

L* = 57.5
a* = 38.8
b* = -16.1
C* = 42.0
H* = 337.5

The pigment prepared according to the Example 2 has been found to have the following CIELAB values:

L* = 59.2
a* = 38.9
b* = -15.1
C* = 41.8
H* = 338.8

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DC* = 0.97
DH* = 1.25
DE* = 1.58

APPLICATION EXAMPLE F

The procedure of Application Example E was followed using a pigment prepared according to the Example 7 of GB 1 868 360 (which has been subjected to the milling process described in Example 2 of this invention). It has been found to have the following CIELAB values:

L* = 58.2
a* = 37.3
b* = -15.3
C* = 40.3
H* = 337.7

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DC* = -1.25
DH* = 0.31
DE* = 1.29

APPLICATION EXAMPLE G

According to the standard DIN 53775A, the preparation of 1% coloured PVC sheet is performed as follows:
100.0 parts of clear PVC are mixed with 1 part of pigment obtained according to the procedure of Example 2 for about 2 minutes. The resulting mixture is passed between two rollers in a rolling mill for 5 minutes, 26 rpm to form a sheet. One of the roller is at a temperature of 178°C and the other is at 163°C. The sheet so obtained is re-rolled at a temperature of 80°C and then pressed between two polished sheets for 0.5 minutes at 165°C.

The L, a, b, C, H colour space values are measured according to the standards DIN 55986 and 6174/CIELAB 76 as described in Application Example A.

The experiment is repeated for Cinquasia Magenta RT-343D and it has been found to have the following CIELAB values:

L* = 32.3
a* = 32.6
b* = 8.4
C* = 33.7
H* = 14.4

The pigment prepared according to the Example 2 has been found to have the following CIELAB values:

L* = 38.7
a* = 44.9
b* = 8.6
C* = 45.8
H* = 10.8

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DL* = 6.26
DC* = 12.50
DH* = -2.11
DE* = 14.14

APPLICATION EXAMPLE H

The procedure of Application Example G was carried out on a pigment prepared according to the Example 7 of GB 1 868 360 (which has been subjected to the milling process described in Example 1 of this invention) and has been found to have the following CIELAB values:

L* = 33.4
a* = 33.6
b* = 6.4
C* = 34.2
H* = 10.8

The colourimetric differences compared to Cinquasia Magenta RT-343D pigment are as follows:

DL* = 1.06
DC* = 0.53
DH* = -2.11
DE* = 2.42

It is clear from the foregoing Application Examples that the pigment prepared according to the Example 2 of this invention has improved properties and can be used to colour solvent-containing and solvent-free plastics materials and plastics resins a bluish-red tone. The resultant fastness properties are very good.

Claims

1. A polymorphic form of 2,9-dichloroquinacridone having an x-ray diffraction pattern including reflections corresponding to the following interplanar spacings and double glancing angles (Grade 2θ):

d-Value (Angstroms)	Grad 2θ
16.73	5.3
6.33	14.0
5.82	15.2
5.36	16.5
4.62	19.2
4.18	21.3
3.88	22.9
3.81	23.3
3.64	24.4
3.52	25.3
3.35	26.6
3.19	27.9
3.08	29.0
2.91	30.7
2.80	31.9
2.68	33.4
2.45	36.7
2.39	37.6
2.28	39.4

2. A polymorphic form of 2,9-dichloroquinacridone described in or with reference to Figure 1 and Figure 2.

3. A process of forming 2,9-dichloroquinacridone comprising the step of reacting 2,5-di(4-chloroanilino)terephthalic acid with concentrated sulphuric acid of a concentration of 90 to 95% at temperatures between 100 to 130°C.

4. A process according to claim 3 wherein the sulphuric acid is at a concentration of 92%.

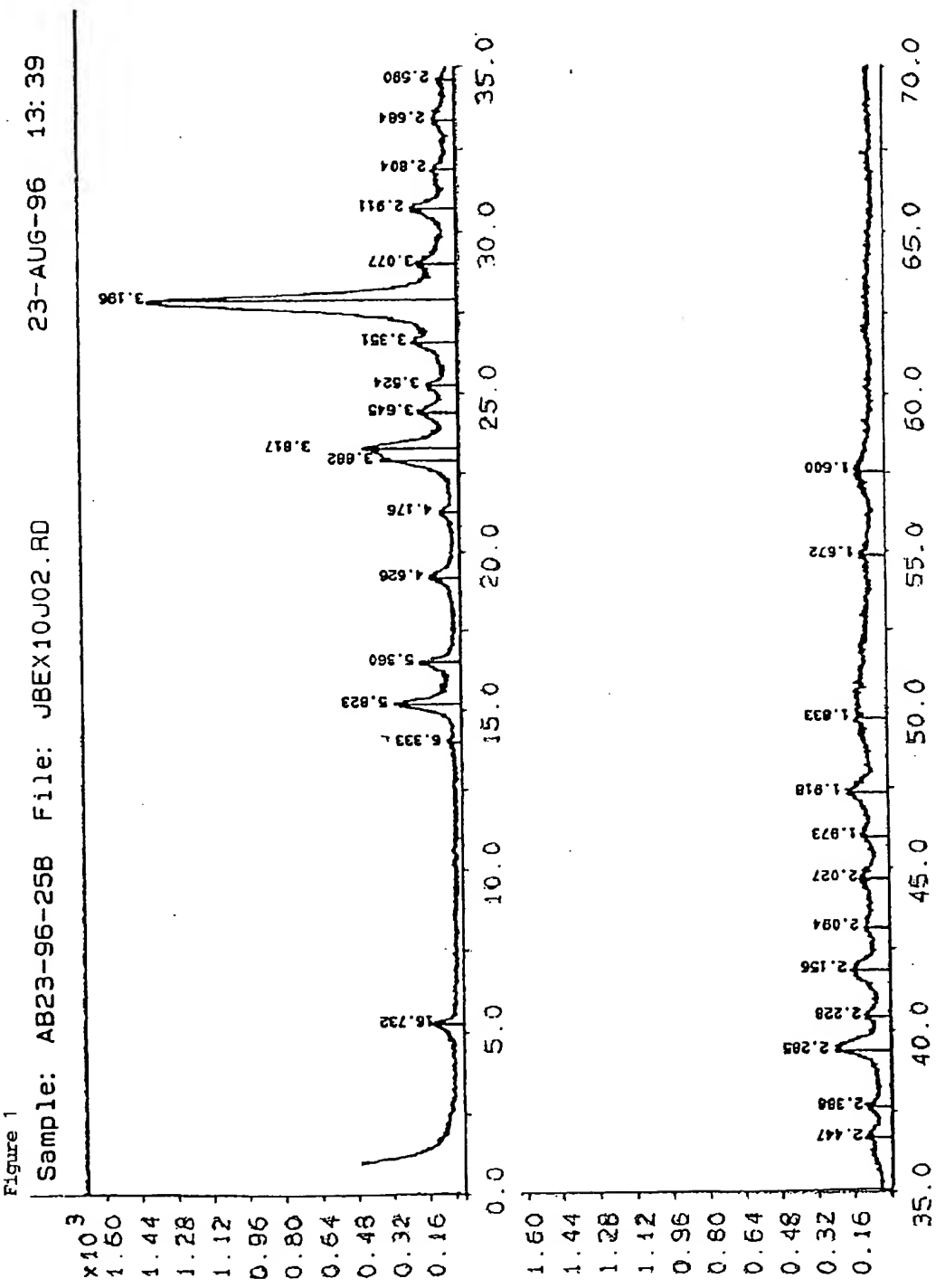
5. A process according to claim 3 or claim 4 wherein the reaction is carried out at a temperature of 110°C.

6. A process according to claim 3 comprising the additional step of milling the 2,9-dichloroquinacridone so formed.

7. 2,9-dichloroquinacridone obtainable by a process according to claim 3.

8. 2,9-dichloroquinacridone obtainable by a process according to claim 6.

Figure 1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1.28
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5.0
10.0
15.0
20.0
25.0
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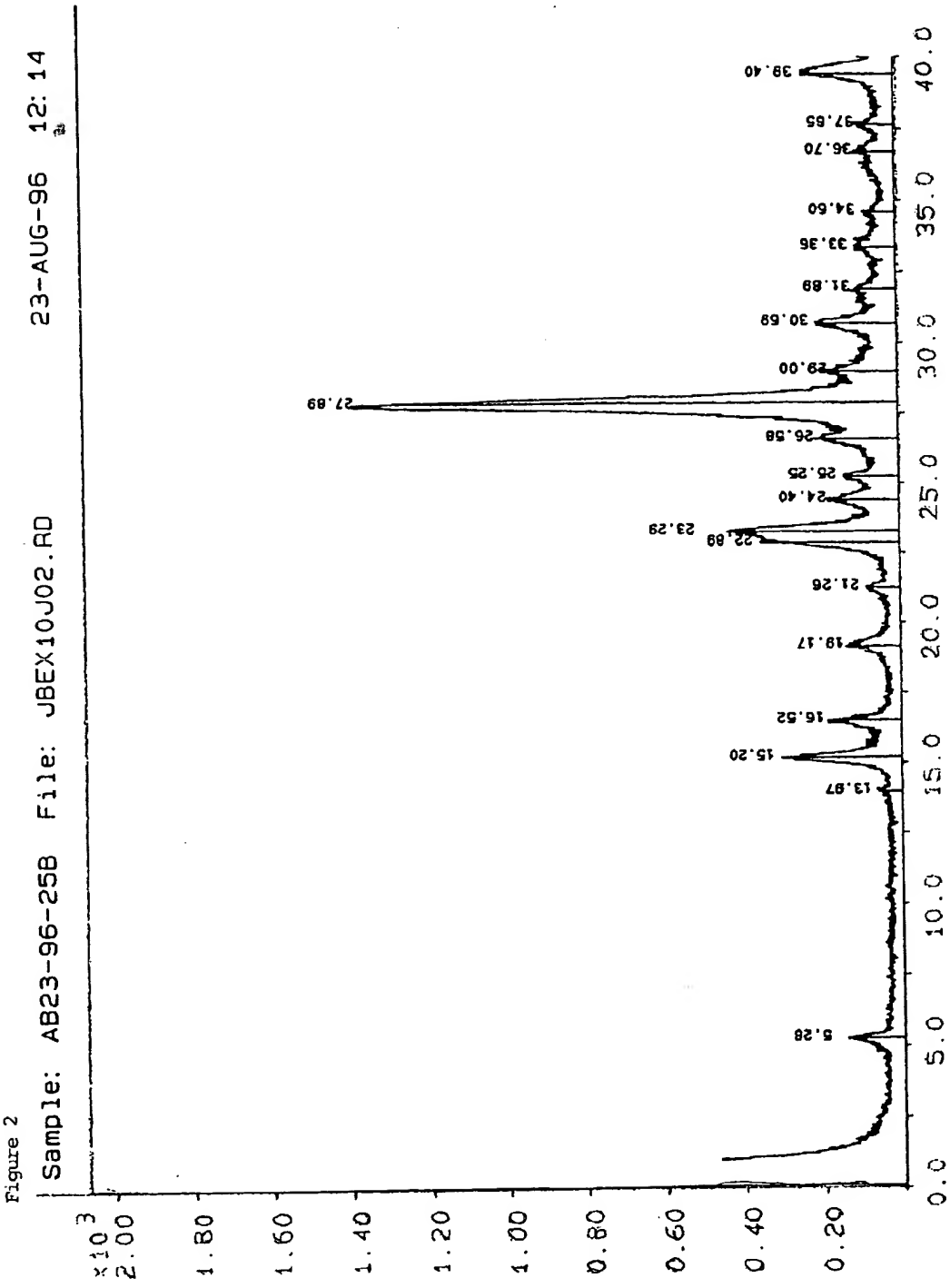
1.572

Figure 2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0.40
0.20
0.0
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10.0
15.0
20.0
25.0
30.0
35.0
40.0
5.28
13.87
15.20
16.52
19.17
21.26
22.89
23.29
24.40
25.25
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27.89
29.00
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33.36
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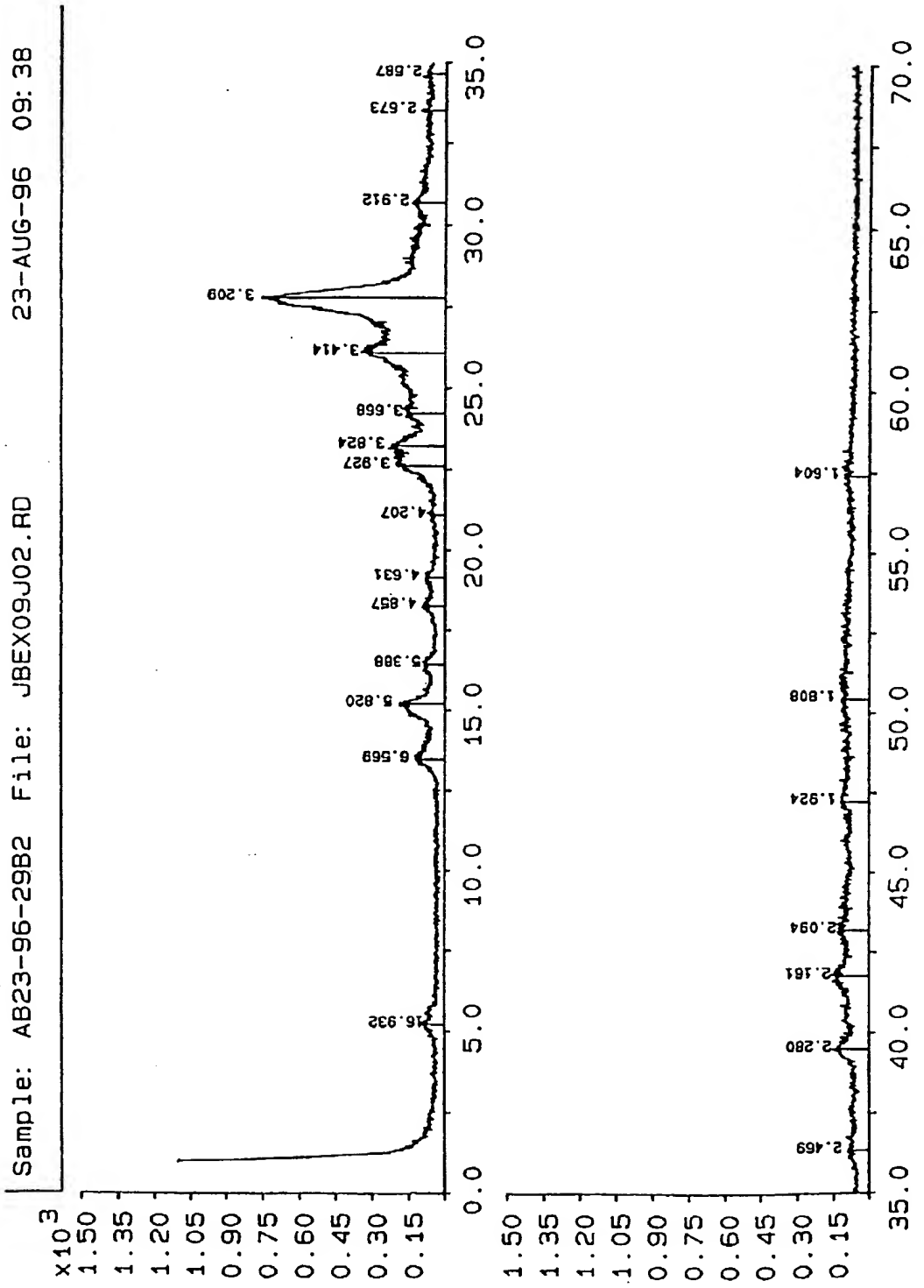
36.70
37.85
38.40

Figure 3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5.388
4.857
4.631
4.207
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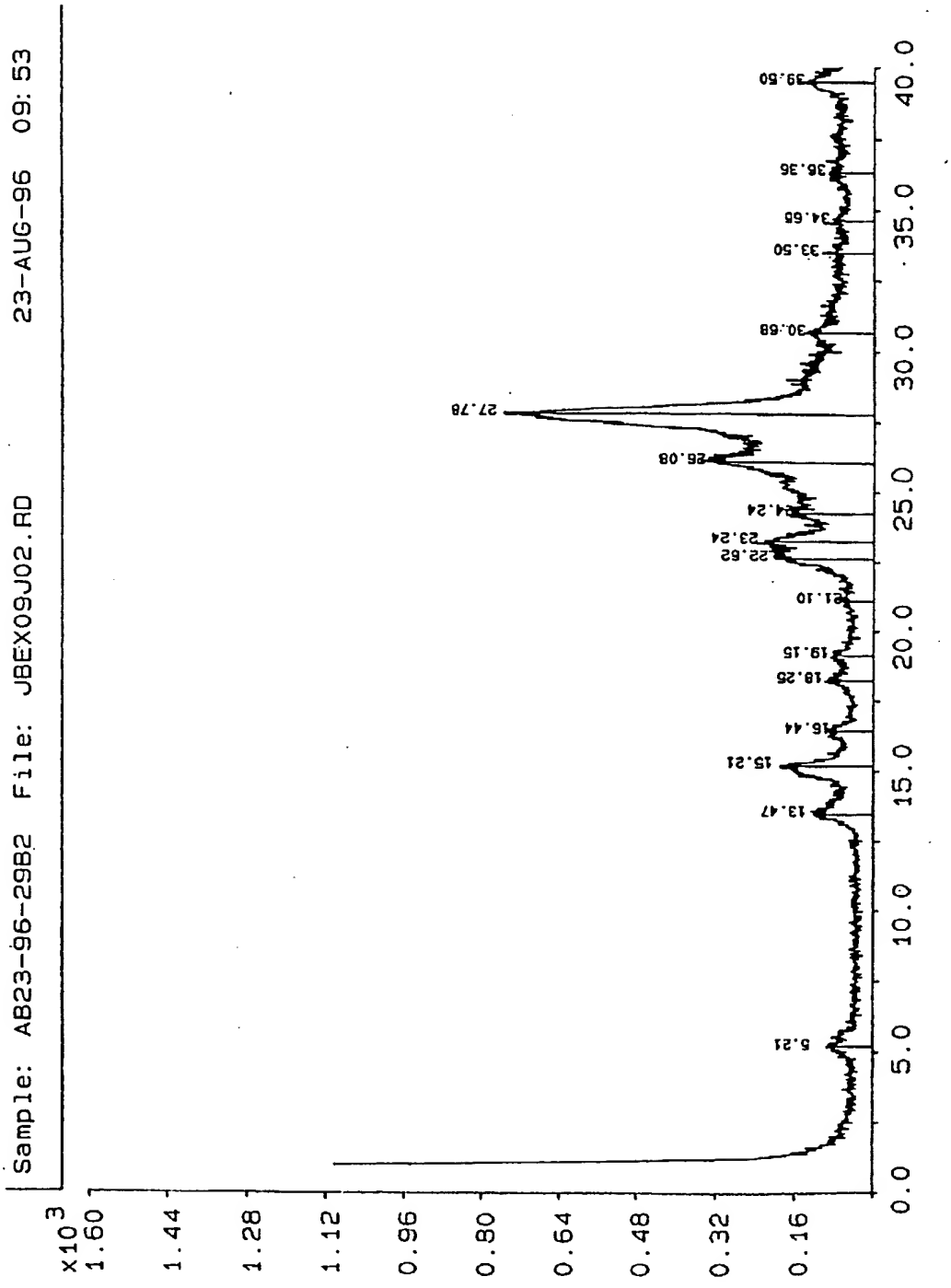
1.604

Figure 4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15.0
20.0
25.0
30.0
35.0
40.0
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19.15
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22.62
23.24
24.24
26.08
27.78
30.68
33.50
34.65
36.36
39.50

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 81 0158

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	FR 1 274 726 A (BASF) 23 February 1962 * page 1, right-hand column, line 23 - page 2, left-hand column, line 11 * * page 3, left-hand column, line 3 - line 20 * * page 3, left-hand column, last paragraph; examples; table 2 *	1-8	C09B48/00 C09B67/52
X	US 3 261 836 A (C.C. CHEN) 19 July 1966 * column 1, line 13 - line 17 * * column 2, line 61 - column 3, line 29; examples 1,10 * * column 9, line 2; table *	1-8	
A	FR 1 226 260 A (CIBA) 11 July 1960 * page 1, left-hand column, paragraph 1 *	1-8	
A	FR 2 137 546 A (SANDOZ SA) 29 December 1972 * the whole document *	1-8	
A	GB 1 020 068 A (BASF) * page 3; example 3 *	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C09B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 June 1998	Dauksch, H

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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PATENT SPECIFICATION

NO DRAWINGS

Date of Application and filing Complete Specification: June 10, 1959.
No. 19910/59.
Two Applications made in Switzerland on June 11, 1958.
Complete Specification Published: May 16, 1962.

Index at acceptance:—Class 2(4), PD1X.
International Classification:—C09b.

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DATA to Q

896,803

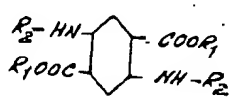
COMPLETE SPECIFICATION

Process for the manufacture of Water-Insoluble Quinacridones Free from Sulphonic Acid Groups

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides a process for the manufacture of water-insoluble quinacridones which are free from sulphonic acid groups and are obtained from 2:5-diarylamino-terephthalic acids.

The invention is based on the observation that compounds of the general formula



in which R_1 represents a hydrogen atom or an aliphatic or aromatic residue and R_2 represents an aryl residue in which at least one ortho-position relatively to the —NH— group is unsubstituted, when heated in the presence of oleum or an acid of the general formula

$$Z—SO_3H$$

(in which Z represents a hydroxyl group or a chlorine atom or an alkyl residue or a residue of the benzene or naphthalene series) react in such manner that a quinacridone is formed accompanied by double ring closure. In the case of sulphuric acid a highly concentrated sulphuric acid of 75—100% strength is used and, when a product containing a sulphonic acid group or sulphonic acid chloride group is formed, such group is split off, by heating it with a dilute mineral acid under superatmospheric pressure.

In the compounds of the above formula used as starting materials the aryl residues R_2 may contain substituents. As 2:5-diarylamino-terephthalic acids and derivatives thereof, of the above general formula there may be used, for example, 2:5 - diphenylamino - terephthalic acid, 2:5 - diphenylamino - terephthalic acid esters and above all substituted 2:5-diphenylamino-terephthalic acids, such as 2:5-di-(methylphenylamino)-terephthalic acids, 2:5-di-(methoxyphenylamino) - terephthalic acids, 2:5 - di - (halogen - phenylamino) - terephthalic acids, 2:5 - di - (nitro - phenyl amino)-terephthalic acid, 2:5 - di - (2^1:4^1-dimethylphenylamino)-terephthalic acid, 2:5-bis - (4^1 - diphenylamino) - terephthalic acid or 2:5 - dianilido - 2^1:4^1:2^{11}:4^{11} - tetrachloroterephthalic acid or 2:5 - (dianilido)-4^1:4^{11}-dimethylterephthalic acid. There may also be used 2:5-diarylamino-terephthalic acids which contain as the aryl residue a polycyclic residue, for example, the residue of phenanthrene or pyrene.

The aforesaid terephthalic acids or derivatives thereof can be obtained by known methods, for example, by the condensation of a succinylosuccinic acid ester with aniline or a substituted aminobenzene, followed by oxidation and, if desired, by hydrolysis.

In general it is of advantage to hydrolyse the terephthalic acid esters before they are used in the process of this invention and therefore to use as starting materials free terephthalic acids or derivatives thereof.

As condensing agents which are reacted with the aforesaid starting materials there may be mentioned, for example, oleum and the following acids: Highly concentrated sulphuric acid of 75—100% strength, sulphuric acid about 90% strength being preferred, and especially sulphuric acid of 90% strength, and chlorosulphonic acid. There may also be used alkyl-, benzene-, toluene- or naphthalene-sulphonic acids, for example, para-bromobenzene sulphonic acid, para-chlorobenzene sulphonic acid, ortho-nitro-

benzene sulphonic acid, meta-nitrobenzene sulphonic acid, ortho-toluene sulphonic acid, α-naphthalene sulphonic acid, β-naphthalene sulphonic acid, carboxyphenzene sulphonic acids and the corresponding chloro-derivatives and especially methane sulphonic acid, meta-benzene disulphonic acid or para-toluene sulphonic acids.

In Annalen *518* pages 245—259 several processes are disclosed for bringing about ring closure of 2:5-diarylamino-terephthalic acids to form quinacridones, such as heating the starting material in the presence of zinc chloride, phosphorus pentachloride, phosphorus pentoxide or aluminium chloride. All these processes have given poor yields and can generally only be used in special cases. On pages 247 and 252-3 of Annalen 518 the cyclization of 2:5 - dinaphthylamino - terephthalic acid or dibenzquinacridone in 73% sulphuric acid as condensing agent is described. The heating of 2:5-diarylamino-terephthalic acid in molten boric acid at a temperature above 300°C (Annalen, Vol. 518, page 245) has hitherto been regarded as the best method. However, this process is extremely difficult to carry out industrially on the one hand, owing to the high temperature used and, owing to the tendency of the boric acid melt to froth during the reaction and to solidify towards the end of the reaction in the form of a non-stirrable mass.

In contradistinction thereto the process of this invention constitutes an industrially simple and cheap process for making water-insoluble quinacridones free from sulphonic acid groups in good yield from terephthalic acids, which it has hitherto been possible to convert by ring closure into quinacridones at best by the process using a boric acid melt.

Furthermore, in contradistinction to the process in which a boric acid melt is used, the process of this invention can be carried out in apparatus of the kind customarily used in the manufacture of dyestuffs.

The reaction conditions used in the process of the invention can be varied within wide limits. The process is advantageously carried out at a temperature substantially above 100°C, for example, within the range of 140 to 200°C.

When the reaction is carried out with sulphuric acid, an excess thereof is generally used, such as about 3 parts of sulphuric acid for every part of 2:5-diarylamino-terephthalic acid. It suffices, however, to react 1 part of sulphuric acid with 1 part of 2:5-diarylamino-terephthalic acid.

When sulphuric acid or chlorosulphonic acid is used, the quinacridones obtained by the process contain sulphonic acid groups. They can be converted into their salts, preferably the sodium salts, and salted out in known manner.

When one of the afore-mentioned organic sulphonic acids is used as condensing agent, the acid can be recovered in the usual manner, either by heating the reaction product *in vacuo* and distilling off the sulphonic acid, or by treating the reaction product with water, separating the solid quinacridone, distilling off the water and recovering the sulphonic acid.

For the elimination of the sulphonic acid groups from quinacridones containing them, the free sulphonic acid or a salt thereof is heated with a dilute mineral acid under super-atmospheric pressure, advantageously mineral acid of 1 to 50% strength, and more especially sulphuric acid of 5% strength is used; the treatment being carried out, for example, for 10 hours at 200°C, whereby the insoluble quinacridones are obtained. The quinacridone obtained in this manner is then recrystallised in the known manner by dissolving it in concentrated sulphuric acid, and then diluting the solution with water to achieve advantageously a sulphuric acid concentration of about 80%.

Alternatively, the quinacridone can be purified in the known manner with alcoholic potassium hydroxide solution.

In a special form of the present process 2:5-diphenylamino-terephthalic acid is reacted with sulphuric acid of 98% strength. The quinacridone obtained in this manner is of violet-red colour. When it is dissolved in concentrated sulphuric acid and then diluted with water, preferably to 85%, the known red α-modification of quinacridone is obtained.

Specification 828,053 describes and claims symmetrical tetrahalogen substituted quinacridones, including 2:4:9:11-tetrachloro-quinacridone. These are prepared by oxidizing the corresponding dihydroquinacridones.

Unless otherwise indicated, parts and percentages in the following Examples are by weight:

Example 1

A mixture of 3 parts of 2:5-diphenylamino-terephthalic acid and 30 parts of concentrated sulphuric acid is heated for 1 hour at 150°C. The solution is then cooled and poured into 300 parts of water. The claret coloured solution is treated with sodium chloride until all the dyestuff has been salted out. The dyestuff is filtered off and washed 3 times with 50 parts of saturated sodium chloride solution on each occasion.

The moist filter cake is heated with 50 parts of sulphuric acid of 5% strength for 10 hours at 200°C in a bomb tube, allowed to cool, and the precipitated quinacridone is filtered off.

For purification 2 parts of the pigment are dissolved in 40 parts of concentrated sulphuric acid at 10 to 20°C. 26.6 Parts of sulphuric acid of 50% strength are then slowly added, and the crystalline product is filtered off, and washed with sulphuric acid of 75% strength and then with water. A brilliant bright-red powder is obtained.

EXAMPLE 2

A mixture of 3 parts of 2:5-diphenylamino-terephthalic acid diethyl ester and 50 parts of sulphuric acid of 90% strength is heated for 2 hours at 160°C. The solution is cooled and then poured into 300 parts of water, and the aqueous solution is treated as described in Example 1. The resulting product has practically the same properties as the product prepared as described in Example 1.

EXAMPLE 3

The reaction described in Example 1 is performed with chlorosulphonic acid instead of with concentrated sulphuric acid.

EXAMPLE 4

120 parts of sulphuric acid of 100% strength are treated at 50°C with 40 parts of 2:5-dianilido-terephthalic acid. The solution is raised to 130° and stirred for 2 hours at this temperature, then cooled to 20°C, and diluted with 680 parts of water. This solution is heated in a porcelain autoclave for 10 hours at 200 to 205°C. The precipitated quinacridone is then filtered off, boiled with sodium hydroxide solution of 5% strength for 1 hour, washed until neutral and dried. Yield: 36 parts of quinacridone.

EXAMPLE 5

2 parts of 2:5-dianilido-2^1:4^1:2^{11}:4^{11}-tetrachloro-terephthalic acid are heated in 40 parts of concentrated sulphuric acid for 15 minutes at 160°C, then cooled to 20°C, the sulphuric acid is diluted to 85% strength and water, and the precipitated 2:4:9:11-tetrachloro-quinacridone is filered off.

EXAMPLE 6

25 parts of 2:5-dianilido-terephthalic acid are stirred in 200 parts of oleum of 24% strength for 1 hour at 25°C. The reaction product is then poured over a mixture of ice and water and the further treatment is as described in Example 1.

EXAMPLE 7

50 parts of concentrated sulphuric acid and 3 parts of 2:5-dianilido-terephthalic ethyl ester are heated in the course of 1 hour to 160°C and then stirred for 2 hours at the same temperature. The solution is poured into water and the further treatment is as described in Example 1.

EXAMPLE 8

25 parts of 2:5-dianilido-terephthalic acid and 250 parts of concentrated sulphuric acid are stirred for 1 hour at 130°C. The solution is then poured into 1250 parts of water, 250 parts of sodium chloride are added, the precipitate is filtered off and washed with a sodium chloride solution of 20% strength until neutral. The filter residue is heated in a porcelain autoclave with 500 parts of sulphuric acid of 5% strength and 25 parts of mercury sulphate for 10 hours at 200 to 205°C. The resulting quinacridone is worked up as described in Example 4.

Instead of 2:5-dianilido-terephthalic acid there may be used 2:5-(2^1-methylphenylamino)-terephthalic acid, 2:5-(2^1:4^1-dimethylphenylamino)-terephthalic acid or 2:5-(dianilido)-4^1:4^{11}-dimethyl-terephthalic acid.

EXAMPLE 9

In the course of ½ hour 25 parts of 2:5-dianilido-terephthalic acid are added to 250 parts of concentrated sulphuric acid heated at 200°C. The solution is then poured into water and the further treatment is as described in Example 1.

EXAMPLE 10

40 parts of 2:5-dianilido-terephthalic acid are added at 50°C to 120 parts of sulphuric acid of 100% strength. The solution is raised to 130°C and stirred for 2 hours at this temperature, then cooled to 20°C and diluted with 300 parts of water. This solution is heated in a porcelain autoclave for 10 hours at 200 to 205°C. The precipitated quinacridone is then filtered off, boiled with sodium hydroxide solution of 5% strength for 1 hour, filtered, washed until neutral and dried. Yield: 36 parts of quinacridone.

EXAMPLE 11

A mixture of 4 parts of 2:5-diphenylamino-terephthalic acid and 40 parts of metanesulphonic acid is heated for ½ hour at 170°C. After cooling, the solution is poured into water, and the precipitated quinacridone is filtered off and boiled with dilute sodium hydroxide solution, it can be further purified by crystallisation from sulphuric acid or by treatment with alcoholic potassium hydroxide solution (Liebig's Annalen *518*, page 245).

Instead of methanesulphonic acid there may be used ethanesulphonic acid or butanesulphonic acid.

EXAMPLE 12

A mixture of 4 parts of 2:5-diphenylamino-terephthalic acid and 40 parts of para-toluenesulphonic acid monohydrate is heated for ½ hour at 160°C and then worked up as described in Example 11. Very pure quinacridone is obtained in a very good yield.

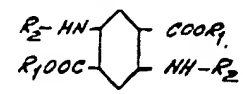
Instead of para-toluenesulphonic acid there may be used benzenesulphonic acid or chlorobenzenesulphonic acid.

EXAMPLE 13

A mixture of 5 parts of 2:5-diphenylamino-terephthalic acid and 50 parts of meta-benzenedisulphonic acid is heated for 2 hours at 150°C and then worked up as described in Example 11.

WHAT WE CLAIM IS:—

1. A process for the manufacture of water-insoluble quinacridones which are free from sulphonic acid groups, wherein a compound of the general formula



in which R_1 represents a hydrogen atom or an aliphatic or aromatic residue, and R_2 repre-

sents an aryl residue in which at least one ortho-position relatively to the —NH— group is unsubstituted, is heated in the presence of oleum or an acid of the general formula Z—SO_3H (in which Z represents a hydroxyl group or a chlorine atom or an alkyl residue or a residue of the benzene or naphthalene series) and, when sulphuric acid is used, a highly concentrated sulphuric acid of 75—100% strength is used and, when a product containing a sulphonic acid group or sulphonic acid chloride group is formed, such group is split off by heating said product with a dilute mineral acid under superatmospheric pressure.

2. A process as claimed in claim 1, wherein the reaction to form the quinacridone is carried out at a temperature within the range of 100°C to 200°C.

3. A process as claimed in claim 1 or 2, wherein 2:5-diphenylamino-terephthalic acid is used as starting material.

4. A process as claimed in claim 1 or 2, wherein a 2:5-diphenylamino-terephthalic acid substituted in the phenyl rings is used as starting material.

5. A process as claimed in any one of claims 1—4, wherein sulphuric acid exceeding 90% strength is used.

6. A process as claimed in any one of claims 1—4, wherein concentrated sulphuric acid containing sulphur trioxide is used.

7. A process as claimed in any one of claims 1—6, wherein there is used for splitting off the sulphonic acid group or groups a dilute mineral acid of 1 to 50 per cent strength.

8. A process as claimed in any one of claims 1—6, wherein the quinacridone sulphonic acid, more especially in the form of a salt thereof, is heated in the presence of dilute sulphuric acid at about 200°C under superatmospheric pressure until the sulphonic acid group or groups are split off and a water-insoluble quinacridone is obtained.

9. A process as claimed in any one of claims 1, 2 and 4 to 8, wherein 2:5-dianilido-$2^1:4^1:2^{11}:4^{11}$-tetrachloro-terephthalic acid is used as starting material and the reaction is carried out at about 160°C.

10. A process as claimed in any one of claims 1 to 4, wherein methane sulphonic acid is used for the reaction.

11. A process as claimed in claim 10, wherein the reaction is carried out at about 170°C.

12. A process as claimed in any one of claims 1—4, wherein the reaction is carried out with para-toluene sulphonic acid.

13. A process as claimed in claim 12, wherein the reaction is carried out at about 160°C.

14. A process as claimed in any one of claims 1—4, wherein the reaction is carried out with meta-benzene disulphonic acid.

15. A process as claimed in claim 14, wherein the reaction is carried out at about 150°C.

16. A process for the manufacture of a water-insoluble quinacridone free from sulphonic acid groups conducted substantially as described in any one of the Examples herein.

17. Water-insoluble quinacridones free from sulphonic acid groups whenever made by the process claimed in any one of claims 1—16.

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